

REMARKS

Applicants would like to thank Examiner Baker for the courteous and helpful discussion held with Applicants' representative on October 10, 2003.

The claimed invention is directed to conjugates containing carriers in which hapten molecules and marker groups or solid phase binding groups are incorporated at specific predetermined positions, such that distances between the hapten molecules and the marker groups or solid phase binding groups are defined thereby. As explained during the interview, the structure of the claimed conjugates is distinct from the structures that result from a random or statistical attachment of moieties, such as when moieties are introduced in the presence of multiple equivalent reaction sites (e.g., in the presence of the multiple carboxylate groups typically found in a chain of amino acids).

As explained during the interview and as described in the specification (e.g., page 6, lines 2-27), the conjugates of the claimed invention contain hapten molecules and marker groups or solid phase binding groups incorporated in the carrier at defined and reproducible positions, such that "[t]he distances between individual groups on the conjugate can be exactly defined and varied if necessary" (page 6, lines 16-18). This ability to define and vary distances is advantageous, for example, in reducing signal quenching and for increasing signal strength of certain marker groups (e.g., page 6, lines 18-27).

The recitation of "predetermined positions" in each of independent claims 72 and 100 refers to the "defined and reproducible positions" described in the specification. To clarify the meaning of this phrase and to obviate any possible misunderstandings, Applicants have amended each of the independent claims to recite that these predetermined positions define distances between the hapten molecules and the marker groups or solid phase binding groups.

Information Disclosure Statement

In accordance with the Examiner's request, copies of the references cited in the Information Disclosure Statement filed on August 21, 2002 are resubmitted herewith.

Claim Rejections - 35 U.S.C. § 112, First Paragraph – Written Description

The written description rejection of claims 80, 101, and 103-106 under 35 U.S.C. § 112, first paragraph has been rendered moot by cancellation of these claims. The written description rejection of claims 72-77, 81, 83-88, and 100 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

Although independent claims 72 and 100 recite language such as “hapten molecules,” “marker groups,” “solid phase binding groups,” and “reactive side groups,” Applicants emphasize that “[t]here is nothing inherently wrong with defining some part of an invention in functional terms” and that “[f]unctional language does not, in and of itself, render a claim improper (e.g., MPEP 2173.05(g), *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)). Applicants respectfully submit that the claimed invention is not dependent upon—and, therefore, should not be limited to—a specific type of hapten molecule, marker group, solid phase binding group or reactive side group provided that the hapten molecules and marker groups or solid phase binding groups are incorporated in the chain at the recited predetermined positions.

Moreover, as noted during the interview, the claim language of “predetermined positions” is not lacking in adequate description, as suggested in the Final Office Action (page 8, section 15), but rather refers to the kind of defined and reproducible arrangement of moieties in a carrier that has been thoroughly described in the specification. For purposes of clarification, each of independent claims 72 and 100 has been rewritten to recite that the “distances between the hapten molecules and the marker groups or solid phase binding groups are defined” by the previously recited “predetermined positions.” This added recitation emphasizes the meaning of the phrase “predetermined positions” as set forth in the specification (e.g., page 6, lines 5-27).

In addition, Applicants note that the use of the terms “hapten molecules,” “marker groups,” and “solid phase binding groups” is widespread in the field of diagnostic assays and the meanings of these terms as well as numerous exemplars thereof and procedures for their use are well-established in the art (in support thereof, Applicants refer to Exhibits A and B submitted with their Response filed July 15, 2002). In addition, all of the functional language is fully supported by and described in the specification as

filed (e.g., page 7, line 33 to page 8, line 35; page 9, lines 5-8; page 9, line 26 to page 11, line 30; page 9, lines 10-16; etc.).

Furthermore, Applicants maintain that while the meaning of the claim term “reactive side groups” would have been clear to one of ordinary skill in the art as referring to any functional groups (e.g., on the carrier) that can react with functional groups of complementary reactivity (e.g., on the haptens, marker groups, or solid phase binding groups) in order to form a bond, each of independent claims 72 and 100 has been rewritten to recite a Markush group of specific reactive side groups.

For at least the reasons set forth above, Applicants respectfully submit that the specification as filed fully satisfied the written description requirement under 35 U.S.C. § 112, first paragraph, and, therefore, respectfully request that this ground of rejection be withdrawn.

Claim Rejections - 35 U.S.C. § 112, First Paragraph – Enablement

The enablement rejection of claims 80, 101, and 106 under 35 U.S.C. § 112, first paragraph has been rendered moot by cancellation of these claims. The enablement rejection of claims 72, 74-77, 81, 83-88, and 100 under 35 U.S.C. § 112, first paragraph is obviated by amendment.

Each of independent claims 72 and 100 has been amended to recite monomeric units that comprise amino acids. Accordingly, Applicants respectfully submit that the enablement rejection of these independent claims, and all claims dependent thereon, under 35 U.S.C. § 112, first paragraph, is rendered moot inasmuch as the Examiner states in the Final Office Action that “the specification ... [is] enabling for conjugates where the polymeric carrier comprises amino acids as the monomeric units” (page 9, section 17).

For at least the reason set forth above, Applicants respectfully submit that the claimed invention is fully enabled. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The rejection of claims 80, 101, 103, and 105-106 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, has been rendered moot by cancellation of these claims. The rejection of claim 85 under 35 U.S.C. § 112, second paragraph, has been obviated by amendment. The rejection of claims 72, 77, 87, and 100 under 35 U.S.C. § 112, second paragraph, is respectfully traversed. As outlined below, each of the phrases identified in paragraphs A, B, C, and E on pages 16-18 of the Final Office Action has been described in the specification and/or has a well-defined meaning within the art. Furthermore, each of the phrases identified in paragraphs D and F on pages 17-18 of the Final Office Action has been eliminated from the claims.

The phrase “solid phase binding groups” refers to groups that can be immobilized to a solid phase during a diagnostic assay (e.g., specification, page 9, lines 5-16). In response to the query on page 16 of the Final Office Action, Applicants confirm that this phrase describes any type of binding interaction between a solid phase binding group and a solid phase, including covalent bond formation and non-covalent interactions (e.g., Hydrogen bonding, van der Waals attractions, etc.). By way of illustration only, one example of the type of immobilization that is referred to by this phrase is embodied in the immobilization of a biotin solid phase binding group on a streptavidin-coated particle surface (e.g., specification, page 27, lines 4-8).

Furthermore, it would have been well understood by one of ordinary skill in the art that the phrase “reactive side groups” refers to any functional groups (e.g., on the carrier) that can react with functional groups of complementary reactivity (e.g., on the haptens, marker groups, or solid phase binding groups) in order to form a bond. Representative examples of reactive side groups suitable for use in accordance with the present invention have been identified in the specification (e.g., page 9, lines 10-16) for purposes of illustration. Moreover, each of independent claims 72 and 100 has been rewritten to recite a Markush group of specific reactive side groups.

In addition, the phrase “non-immunologically reactive” has been eliminated from independent claim 72 and is now recited in only the new dependent claim 110. As used

in claim 110, the phrase refers to “an amino acid sequence which does not interfere with the test procedure in the intended application of the conjugate as an antigen in an immunological method of detection” (specification, page 16, lines 3-8), and would have been well understood by one of ordinary skill in the art. Applicants agree with the Examiner’s statement that “[a] conjugate may be ‘immunologically reactive’ in one assay and ‘non-immunologically reactive’ in another” (Final Office Action, page 17, section C) but maintain that the decision as to whether a particular carrier would be suitable for a given assay lies well within the skill of an ordinary artisan in this field.

Although Applicants maintain that the recitation in claim 85 that “the polymeric carrier has a helical structure” would have been clear to one of ordinary skill in the art, the rejection of claim 85 has been rendered moot by the elimination of this recitation from the claim.

The phrase “pharmacologically active” is a term of art used routinely in the field of chemistry and pharmacology and is generally synonymous with the phrase “biologically active.” Both phrases refer to the interaction of a drug with some kind of receptor in a subject (see Exhibit 1 attached herewith, which is excerpted from *Medicinal Chemistry: A Biochemical Approach, 2nd Edition* by Thomas Nogrady, Oxford University Press, New York, 1998, page 40). It is well understood by those of ordinary skill that a non-negligible level of pharmacological activity presupposes a molecular species having sufficiently complementary structure, electronic environment, etc. to those of the receptor. Applicants intend the phrase “pharmacologically active” to be interpreted in its conventional sense and believe that the meaning of the phrase would have been abundantly clear to those of ordinary skill in the art.

The rejection of claim 101 for its recitation of the term “alike” has been rendered moot by the cancellation of this claim. Applicants note that new claim 107, which is based on canceled claim 101, recites that “the side groups through which the hapten molecules and the marker groups or the solid phase binding groups are bound to the carrier are either amino groups or thiol groups.” This recitation is unambiguous.

For at least the reasons set forth above, Applicants respectfully submit that the present claims are not indefinite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 102

The rejection of claims 80, 101, 103, and 105-106 under 35 U.S.C. § 102(b) as being anticipated by *Bredehorst et al.* (Anal. Biochem., 1991) has been rendered moot by cancellation of these claims. The rejection of claims 72, 74-77, 81, 83, and 86-87 under 35 U.S.C. § 102(b) as being anticipated by *Bredehorst et al.* has been obviated by amendment.

Each of independent claims 72 and 100 recites that the hapten molecules and the marker groups or the solid phase binding groups are bound to the carrier through a side group selected from the group consisting of amino groups, thiol groups, and a combination thereof. In contrast to the conjugates of the claimed invention, the side groups described in *Bredehorst et al.* are limited to a single terminal amino group for attachment of the hapten, three carboxyl groups for attachment of the flurophores, and four sulfhydryl groups (e.g., sulfonates) for attachment of the hydrophilic residues (e.g., page 272, column 1, abstract; page 273, column 1, first paragraph; pages 274-275, bridging paragraph). *Bredehorst et al.* contains no teaching or suggestion of the Markush group required by the claimed invention.

For at least this reason, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Bredehorst et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 80, 101, 103, and 105-106 under 35 U.S.C. § 102(b) as being anticipated by *Buchardt et al.* (WO 92/2073) has been rendered moot by cancellation of these claims. The rejection of claims 72, 74-75, 77, 81, 83, 86-87, and 100 under 35 U.S.C. § 102(b) as being anticipated by *Buchardt et al.* is respectfully traversed.

Buchardt et al. describes nucleic acid analogues for use in diagnostic and analytical procedures (e.g., page 3, lines 9-30). The nucleic acid analogues described in *Buchardt et al.* are peptide nucleic acids in which ligands (primarily nucleobases) are attached directly or indirectly to nitrogen atoms in the backbone (e.g., abstract; page 3,

lines 13-21). *Buchardt et al.* does not teach or suggest conjugates containing amino acids as the monomeric units in which hapten molecules and marker groups or solid phase binding groups are coupled to the carrier through reactive side groups selected from the group consisting of amino groups, thiol groups, and a combination thereof, as required by the claimed invention.

For at least this reason, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Buchardt et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 80 and 106 under 35 U.S.C. § 102(b) as being anticipated by *Tam* (U.S. Patent No. 5,229,490) has been rendered moot by cancellation of these claims. The rejection of claims 72, 74-75, 86-88, and 100 under 35 U.S.C. § 102(b) as being anticipated by *Tam* is respectfully traversed.

Tam does not teach or suggest at least one element of independent claims 72 and 100. Namely, *Tam* does not teach or suggest conjugates containing hapten molecules and marker groups or solid phase binding groups coupled to reactive side groups on the carrier.

Tam describes multiple antigen peptide systems in which multiple antigens may be attached to a carrier (e.g., col. 4, lines 56-60). *Tam* does not teach or suggest a carrier that simultaneously contains both a hapten molecule (e.g., a peptide antigen) and a solid phase binding group in such a way as to meet all of the recited elements of the claimed invention. As noted during the interview, if the Gly-OH residue described in *Tam* were regarded as a solid phase binding group in the sense of the claimed invention, as proposed in the Final Office Action (page 28, section 45), then at least one element recited in each of the independent claims would still not be satisfied—namely, that hapten molecules and marker groups or solid phase binding groups be incorporated in the carrier at predetermined positions, such that “distances between the hapten molecules and the marker groups or solid phase binding groups are defined thereby. The reasons are that the hydroxyl group (i.e., -OH) at the C-terminus of a peptide chain is part a carboxylic acid group (i.e., -COOH)—not a free alcohol—and that

the carboxylic acid group does not appear exclusively at the C-terminus of a peptide. Rather, the carboxylic acid may appear elsewhere, such as in glutamate and aspartate residues. Thus, in such a system, there would exist multiple equivalent functional groups available to react with a solid phase and, therefore, a statistical distribution of products would be expected. In other words, coupling to the carrier would take place randomly and not at predetermined positions as required by the claimed invention. As explained during the interview, Applicants respectfully disagree with the statement in the Final Office Action (page 30, section 48) that “the features upon which applicant relies (i.e., controlled incorporation) are not recited in the rejected claim(s).” Applicants submit that these distinguishing features are encompassed by the recited phrase “predetermined positions” and by the added recitation that the “distances between the hapten molecules and the marker groups or solid phase binding groups are defined” by these predetermined positions.

Applicants further note that *Tam* also does not teach or suggest a carrier that simultaneously contains both a hapten molecule (e.g., a peptide antigen) and a marker group (e.g., a diagnostic moiety). Rather, as is evident from the description in *Tam* (e.g., col. 10, lines 27-34), the diagnostic agent described in *Tam* is intended to be used as an alternative to the peptide antigen and the carriers described therein would not contain both a peptide antigen and a detectable marker at the same time. For example, *Tam* states that: “This invention has been described principally as it is applied to the production of vaccines based on peptide antigens. However, as will be apparent to those skilled in the art, it is not limited to such products. For example, the core molecule could be used as a carrier for ... a diagnostic agent” (col. 10, lines 27-34).

For at least these reasons, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Tam*. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 80 and 106 under 35 U.S.C. § 102(e) as being anticipated by *Rose et al.* (US 6,001,364) has been rendered moot by cancellation of these claims.

The rejection of claims 72, 74-76, 86-88, and 100 under 35 U.S.C. § 102(e) as being anticipated by *Rose et al.* is respectfully traversed.

Rose et al. does not teach or suggest at least one element recited in each of independent claims 72 and 100—namely, that hapten molecules and marker groups or solid phase binding groups be coupled to reactive side groups on a carrier at predetermined positions.

Rose et al. describes structures having a baseplate attached to a plurality of organic molecules through a plurality of oxime linkages (e.g., col. 2, line 62 to col. 3, line 10). If, *arguendo*, the baseplates described in *Rose et al.* were regarded as polymeric carriers in the sense of the claimed invention and the so-called “complementary orthogonal specifically active molecules” (COSMs) attached thereto via oxime linkages were regarded as haptens in the sense of the claimed invention, as suggested in the Final Office Action (e.g., page 30, section 50), then at least one element of the claimed invention—namely, that a further 1-10 marker groups or 1-10 solid phase binding groups be attached to the baseplate at predetermined positions— would still be lacking. As noted above and as explained during the interview, Applicants respectfully disagree with the statement in the Final Office Action (page 33, section 53) that “the features upon which applicant relies (i.e., controlled incorporation) are not recited in the rejected claim(s).” Applicants submit that these distinguishing features are encompassed by the recited phrase “predetermined positions” and by the added recitation that the “distances between the hapten molecules and the marker groups or solid phase binding groups are defined” by these predetermined positions.

As is evident from the description in *Rose et al.*, the attachment of moieties to the baseplate structure would not satisfy the claim requirement for predetermined positions inasmuch as the baseplate structures provide multiple equivalent reaction sites that would lead to the type of statistical attachments described above. For example, the conjugate shown in Figure 1 of *Rose et al.*, which is cited in the Final Office Action (page 31), has a plurality of carboxylic acid moieties throughout the peptide chain that would compete in chemical reactivity with the terminal “hydroxyl group” for attachment to a solid phase. The reasons are that the terminal “hydroxyl group” at the C-terminus of a peptide chain is part a carboxylic acid group (i.e., -COOH)—not a free alcohol (i.e.,

-OH)—and that the carboxylic acid group does not appear exclusively at the C-terminus of the chain. Rather, as is evident from Figure 1, the carboxylic acid group appears throughout the chain, such as in the internal glutamate residues (denoted by E). Thus, in such a system, multiple equivalent functional groups are available to react with the solid phase and, therefore, a statistical distribution of products would be expected. In other words, as noted above, coupling to the carrier would take place randomly and not at predetermined positions as required by the claimed invention. In short, *Rose et al.* contains no teaching or suggestion of the predetermined positions required by the claimed invention.

For at least these reasons, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Rose et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

The rejection of claims 80, 103-104, and 106 under 35 U.S.C. § 103(a) as being unpatentable over *Tam* has been rendered moot by the cancellation of these claims. The rejection of claims 72, 74-75, 81, 86-88, and 100 under 35 U.S.C. § 103(a) as being unpatentable over *Tam* is respectfully traversed.

As noted above, *Tam* does not teach or suggest the entire combination of elements recited in the claimed invention. By way of example, *Tam* does not teach or suggest a carrier that simultaneously contains both a hapten molecule and a solid phase binding group in such a way as to meet all of the recited elements of the claimed invention (e.g., that incorporation be at predetermined positions) nor does *Tam* teach or suggest a carrier that simultaneously contains both a hapten molecule and a marker group. Thus, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Tam*. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 80, 103, and 106 under 35 U.S.C. § 103(a) as being unpatentable over *Rose et al.* has been rendered moot by the cancellation of these

claims. The rejection of claims 72-76, 81, 86-88, and 100 under 35 U.S.C. § 103(a) as being unpatentable over *Rose et al.* is respectfully traversed. As noted above, *Rose et al.* does not teach or suggest the entire combination of elements recited in the claimed invention. By way of example, *Rose et al.* does not teach or suggest conjugates containing hapten molecules and marker groups or solid phase binding groups at predetermined positions on a carrier. Thus, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of *Rose et al.* Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 80, 101, 103, and 105-106 under 35 U.S.C. § 103(a) as being unpatentable over *Bredehorst et al.* in view of *Bard* (US 5,310,687) has been rendered moot by cancellation of these claims. The rejection of claims 72-77, 81, 83-84, and 86-87 under 35 U.S.C. § 103(a) as being unpatentable over *Bredehorst et al.* in view of *Bard* (US 5,310,687) has been obviated by amendment. As noted above, *Bredehorst et al.* does not teach or suggest the Markush group of reactive side groups required by the claimed invention. Likewise, *Bard*, which describes luminescent metal chelate labels and means for detection, does not contain any teaching or suggestion of the recited side groups. Thus, inasmuch as the combination of *Bredehorst et al.* and *Bard* does not teach or suggest all of the recited elements of the claimed invention, Applicants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of these references. Accordingly, withdrawal of this ground of rejection is respectfully requested.

New Claims:


New dependent claims 107-115, all of which depend from independent claim 72, recite specific types of hapten molecules, marker groups or solid phase binding groups that have been described in the specification. Inasmuch as independent claims 72 is believed to be allowable for at least the reasons set forth above, Applicants respectfully submit that dependent claims 107-115 are likewise allowable.

Conclusion:

In view of the Amendments and Remarks set forth above, Applicants respectfully submit that the claimed invention is in condition for allowance. Early notification to such effect is earnestly solicited.

If for any reason the Examiner feels that the above Amendments and Remarks do not put the claims in condition to be allowed, and that a discussion would be helpful, it is respectfully requested that the Examiner contact the undersigned agent directly at (312)-321-4257.

Respectfully submitted,



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7. CHEMICAL BONDING AND BIOLOGICAL ACTIVITY

In molecular terms, the activity of drugs is initiated by their interaction with some kind of receptor. Since the association of small molecules (e.g., drugs) with macromolecules (e.g., receptors) is promoted and stabilized by bond formation, an understanding of the nature and combination of various chemical bonds is of great interest to the medicinal chemist. As discussed earlier, covalent and noncovalent bonds are both based on electronic interactions but differ greatly in their stability, which is expressed in terms of the bond dissociation energy. Table 1.4 summarizes the various types of bonds and their average bond energies. Although there is no direct correlation between bond energy and drug potency, the energy values give an approximate estimate of the ease of formation and disruption and of the relative strengths of various bond types.

Table 1.4. Chemical bonds and average bond energies

Bond type	Example	Total interaction energy, $-\Delta E$ (kJ/mol)	Electrostatic energy, $-\Delta E_{es}$ (kJ/mol)	Charge-transfer energy, ΔE_{ct} (kJ/mol)
Dispersion (van der Waals)	Xe...Xe	1.9	0	0
Hydrophobic	C ₆ H ₆ ...C ₆ H ₆	4.2	≠0	≠0
Hydrogen	H ₂ O...H ₂ O	37	38	9
Charge transfer	$ \begin{array}{c} \text{NC} \quad \text{CN} \\ \diagdown \quad \diagup \\ \text{C} \\ \parallel \\ \text{C} \rightarrow \text{H}_2\text{O} \\ \diagup \quad \diagdown \\ \text{NC} \quad \text{CN} \end{array} $	17	16	4
Dipole-dipole	$ \begin{array}{c} >\text{C}=\text{O} \\ \\ -\text{NR}_3 \end{array} $	~5		
Ion-dipole	F [⊖] ...H ₂ O	171	154	75
Ionic	NH ₄ [⊕] F [⊖]	685	757	149
	H [⊕] Cl [⊖]	450		
Covalent	$ \begin{array}{c} \diagdown \quad \diagup \\ \text{C}-\text{C} \\ \diagup \quad \diagdown \end{array} $	346		
	$ \begin{array}{c} \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \end{array} $	614		

Modified from Stenlake (1979) and Kollman (1980).

Van der Waal based on polar atom by a nucleophile to induce induced dipole atoms, this noncovalent where R is the group operate with the force of less than 1 kcal/mol interactions.

While inducing a system, a large amount of energy is required. In the case of $-\text{CH}_2-$ groups they can pack closely and form bonds or branches. Hydrophilic substituted groups are more effective in binding better to the receptor.

Hydrophobic proteins, in the case of their receptor, first introduce low solubility hydrocarbon bonds with the nonpolar molecule. The liquid bond is of order in the case of the hydrophobic. When the hydrophobic molecules diffuse in the water molecule, the longer part of the molecule is in an entropically unfavorable state by about 3 kcal/mol energy because the hydrophobic effect is operative but has not been questioned.